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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,727	01/23/2004	Mark William Bodmer	674525-2010	2653
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EXAMINER				
BUNNER, BRIDGET E				
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/765,727

Applicant(s)

BODMER ET AL.

Examiner

Bridget E. Bunner

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 April 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8, 10, 12, 14 and 21-38 is/are pending in the application.
- 4a) Of the above claim(s) 8, 10, 12, 14, 31 and 32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-30 and 33-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 8, 10, 12, 14, 21-38 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 January 2004 and 28 September 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-646)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

The amendment of 11 April 2008 has been entered in full. Claims 21-30 are amended. Claims 1-7, 9, 11, 13, 15-20 are cancelled. Claims 33-38 are added.

It is noted that after further consideration by the Examiner, the restriction requirement (07 March 2007) between Group III, drawn to administration of a cell in which cytokine expression is modified by a modulator of Notch signaling, and elected Group I (drawn to contacting a cell with a modulator of Notch signaling) is hereby *withdrawn*.

Claims 8, 10, 12, 14, and 30-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07 August 2007.

Claims 21-30 and 33-38 are under consideration in the instant application.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pages 3-4 of the previous Office Action (16 October 2007) are *withdrawn* in view of the amended specification (11 April 2008).

Art Unit: 1647

2. The objection to claims 2-7, 9, 11, 13, 17-22, 24, and 27-30 10 at page 4 of the previous Office Action (16 October 2007) is *withdrawn* in view of the amended and cancelled claims (11 April 2008).
3. The rejections of claims 1-7, 9, 11, 13, and 15-30 under 35 U.S.C. 112, second paragraph, as set forth at pages 4-5 of the previous Office Action (16 October 2007) are *withdrawn* in view of Applicant's persuasive arguments and the amended and cancelled claims (11 April 2008).
4. The rejections of claims 1-7, 9, 11, 13, 15, and 17-20 under 35 U.S.C. § 102(b) as set forth at pages 14-16 of the previous Office Action (16 October 2007) are *withdrawn* in view of the cancelled claims (11 April 2008).
5. The rejection of claims 1-7, 9, 11, 13, and 15-30 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pages 10-13 of the previous Office Action (16 October 2007) is *withdrawn* in view of Applicant's persuasive arguments and cancelled claims (11 April 2008).
6. The provisional rejection of claims 1, 15-20, 28-30 on the ground of nonstatutory obviousness-type double patenting is *withdrawn* in view of the abandonment of application 11/178,724.
7. The provisional rejection of claims 22-23 and 27 on the ground of nonstatutory obviousness-type double patenting is *withdrawn* in view of the abandonment of application 11/071,796.

Claim Objections

8. Claims 33-34, 36, 37 are objected to because of the following informalities:
9. Claims 33-34, 36, 37 use the acronyms "TNF α ", "IL-5", "IL-13", "TH2", and "TH1", without first defining what they represents in the independent claims. While the claims can

reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 21-30 and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth for claims 21-27 at pages 6-10 of the previous Office Action (16 October 2007).

The claims are directed to methods for reducing a TH2 and TH1 immune response in a subject in need thereof comprising (i) contacting a cell of the immune system with a modulator of Notch signaling to modify cytokine expression in the cell; and (ii) administering said cell in which cytokine expression is modified, to the subject. The claims recite a method for treating inflammation, an inflammatory condition or an autoimmune condition comprising (i) contacting a cell of the immune system with a modulator of Notch signaling to modify cytokine expression in the cell; and (ii) administering said cell in which cytokine expression is modified, to the subject. The claims recite a method for modifying cytokine expression in cells of the immune system of a patient in need thereof comprising administering a modulator of Notch signaling to

said patient to modify cytokine expression of said patient's cells *in vivo*. The claims recite a method for modifying cytokine expression in cells of the immune system of a patient in need thereof comprising (i) administering a modulator of Notch signaling to the cells of said subject *ex vivo*; and (ii) administering said cells in which cytokine expression is modified to the subject. Finally, the claims recite a method for treating a disease associated with excessive TNF α production, excessive IL-5 production or excessive IL-13 production, comprising (i) contacting a cell of the immune system with a modulator of Notch signaling to modify cytokine expression in the cell; and (ii) administering said cell in which cytokine expression is modified, to the subject. Claims 33-38 are directed to methods of administering a modulator of Notch signaling to a subject in need thereof.

Applicant's arguments (11 April 2008), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 12 of the Response, Applicant asserts that the claim amendments clarify the invention and modify the scope of the claims. Applicant points out that the cells of the claims are recited as being cells of the immune system, which are described in the specification (page 52, line 17 through page 54, line 7). Applicant also contends that the specification provides substantial guidance for performing the claimed methods of the invention. Applicant states that the specification describes screening assays for determining modulators of Notch signaling (pages 34-35, 65-66). Applicant indicates that the specification discloses cytokines which experience modified expression and describes administration of modulators of Notch signaling and cells. Applicant also argues that the working examples, particularly Example 5, demonstrate how the methods can be applied to modify cytokine expression in cells. Applicant concludes

that the skilled artisan can apply these teachings to reducing TH1 and TH2-mediated immune responses. At page 13 of the Response, Applicant submits that a skilled person would appreciate from the description and from the results of the experiments in the Examples how to perform the steps of modifying cytokine expression *in vivo*, *ex vivo*, and *in vitro*. Applicant asserts that while the experiments were performed using mouse and human CD4+ cells, mouse CD4+ TH1 and TH2 polarised cells and cell lines, the skilled artisan would appreciate from the specification how to modify the cells for the claimed methods. Applicant contends that one skilled in the art can determine the dosages and routes of administration without undue experimentation as such work is routine. Applicant also states that the skilled artisan can apply the teachings of the modulators of Notch signaling, the cytokines, etc., in the specification to perform the steps of the invention.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that the instant specification teaches that cells of the immune system include, for example, antigen presenting cells (APCs), T cells, B cells, and dendritic cells (pages 52-53). However, as discussed at the bottom of page 7 of the previous Office Action (16 October 2007), the specification does not teach the administration of any immune system cell in which cytokine expression is modified or the administration of any modulator of Notch signaling to any subject. A large quantity of experimentation would be required of the skilled artisan to determine the optimal dosage, duration, and route of administration of the cells and all possible Notch modulators. Although Applicant asserts that the specification describes screening assays for modulators and methods for administration of Notch modulators and cells, the specification only outlines prophetic procedures for such. There is little guidance or methods disclosed in the

specification to indicate that any cell of the immune system in which Notch is modulated, as well as any Notch modulator, reduces a TH1 response, reduces a TH2 response, treats diverse conditions or diseases, and modifies cytokine expression in cells of the immune system *in vivo*. The disclosed methods are not adequate guidance, but are merely an invitation for the artisan to use the current invention as a starting point for further experimentation. According to MPEP § 2164.06, “the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis”.

Additionally, Example 5 of the specification teaches culturing various lymphocytes (such as TH1 and TH2 cells) in the presence and absence of Notch ligand (Delta-Fc) and measuring cytokine production (Figure 9; pages 95-96, 97-98). The Examiner acknowledges that the fusion protein, Delta-Fc, alters the expression of IL-10, IL-13, IFN γ , and IL-2 in TH1 and TH2 cells *in vitro*. However, the scope of the instant claims is much broader than Example 5 and encompasses the *administration* of any Notch modulator or cell that has been contacted with any Notch modulator *to a subject*, modification of any cytokine expression profile, and treatment of a plethora of diverse diseases or disorders. As discussed in the previous Office Action, McKenzie et al. (Sem Cell Dev Biol 14: 127-134, 2003) teach that “in mammalian systems, little is known about the extent to which different Notch ligands activate different receptors under physiological conditions, and whether there are distinct downstream signaling events triggered by different ligand/receptor combinations” (page 128, column 1, 1st paragraph). Also, the various diseases

and conditions encompassed by the instant claims and disclosed in the specification have different pathophysiology. Thus, one skilled in the art would not be able to predict that all possible modulators of Notch or cells contacted with all possible Notch modulators would reduce a TH1 immune response; reduce a TH2 immune response; treat inflammation, an inflammatory condition, or an autoimmune condition; or treat a disease associated with excessive TNF α production, excessive IL-5 production, or excessive IL-13 production, as required by the instant claims. Based on the teachings of unpredictability regarding *in vivo* therapy which are taught in the art, persons skilled in the art would not associate *in vitro* results with *in vivo* therapeutic efficacy. Applicant's specification fails to contain sufficient disclosure to overcome the teachings of unpredictability which are found in the art. *Ex parte Balzarini* 21 USPQ2d 1892 (BdPatApp&Int. 1991).

Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily reduce a TH1 immune response; reduce a TH2 immune response; treat inflammation, an inflammatory condition, or an autoimmune condition; or treat a disease associated with excessive TNF α production, excessive IL-5 production, or excessive IL-13 production by administration of a Notch modulator or a cell of the immune system contacted with a Notch modulator.

Art Unit: 1647

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to administer all possible Notch modulators or cells of the immune system contacted with a Notch modulator to reduce a TH2 immune response, reduce a TH1 immune response, treat an inflammatory or autoimmune condition, and treat a disease associated with excessive production of TNF α , IL-5, or IL-13; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; the unpredictability of the *in vivo* effects of Notch modulators or cells of the immune system on the reduction of a TH2 immune response, reduction a TH1 immune response, treatment an inflammatory or autoimmune condition, and treatment a disease associated with excessive production of TNF α , IL-5, or IL-13; and the breath of the claims which fail to recite limitations for Notch modulators undue experimentation would be required of the skilled

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 25, 28-30, 33-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamb et al. ("Lamb1"; WO 98/20142; 14 May 1998).

Lamb1 teach that by exposing a population of naïve T cells to a Notch-ligand expressed by an antigen presenting cell (APC) cell in the presence of an allergen or antigen, the Notch-

ligand is capable of making the T cell population tolerant to said allergen or antigen (page 4, lines 8-12). Lamb1 disclose that diseases or infectious states that are mediated by T cells and may be treated with use of the appropriate allergen or antigen and Notch-ligand include asthma, allergy, graft rejection, autoimmunity, tumor induced aberrations to the T cell system, and infectious diseases (page 8, lines 17-25). Lamb1 teach that the Notch-ligands (which activate Notch) used are preferably Delta or Serrate family members (page 10, lines 21-24). Lamb1 teach that Notch ligands have a diagnostic DSL domain comprising 20-22 amino acids at the amino terminus of the protein and between 3-8 EGF-like repeats on the extracellular surface (page 2, lines 12-14). It is noted that at the time the instant invention was made, it was well-known in the art that diseases and disorders, such as asthma, allergy, graft rejection, autoimmunity, tumor induced aberrations to the T cell system, and infectious disease, were associated with Th1/Th2 immune responses and excessive cytokine production by cells of the immune system (see for example, Spellberg et al. Clin Infect Disease 32: 76-102, 2001; Barnes, P.J., J Allergy Clin Immunol 108: S72-S76, 2001; Dong et al. Curr Opin Hematol 8:47-51, 2001). Thus, Lamb1 anticipate the claimed invention of the instant application.

12. Claims 21-24, 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamb et al. ("Lamb2"; WO 00/36089; 22 June 2000).

Lamb2 teach that incubating antigen presenting cells (APCs) and lymphocytes, e.g., T cells, in the presence of substances that upregulate expression of genes encoding Notch or Notch ligands, and a specific antigen produces APCs capable of inducing immunological tolerance in such lymphocytes or other APCs to the specific antigen (page 2, lines 9-12). Lamb2 disclose

Art Unit: 1647

that the resulting primed APCs and lymphocytes may be administered to a recipient individual to induce immunotolerance to the specific antigen or to treat or prevent a range of immune disorders characterized by inappropriate lymphocyte activity, such as Th1/Th2 cell activity, autoimmune disease and graft rejection (page 2, lines 13-21; page 20, lines 15-29; pages 27-30). Lamb2 disclose that particular conditions that may be treated or prevented include rheumatoid arthritis, allergies, asthma, and graft rejection (page 20, lines 31-33; page 21, lines 1-21). It is noted that at the time the instant invention was made, it was well-known in the art that diseases and disorders, such as rheumatoid arthritis, allergies, asthma, and graft rejection, were associated with Th1/Th2 immune responses and excessive cytokine production by cells of the immune system (see for example, Spellberg et al. Clin Infect Disease 32: 76-102, 2001; Barnes, P.J., J Allergy Clin Immunol 108: S72-S76, 2001; Dong et al. Curr Opin Hematol 8:47-51, 2001). Thus, Lamb2 anticipate the claimed invention of the instant application.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
02 July 2008

/Bridget E Bunner/
Primary Examiner, Art Unit 1647